REMARKS

Status of the Claims

Claims 1-12, 14-25, 27-45, 47 and 48 were pending and claims 1-12, 14 and 43-45 are under active examination. By amendment herein, claim 1 has been amended to incorporate the limitations of previous claims 3 and 6-8, which have been canceled without prejudice or disclaimer. Claims 2, 11, 16, 19-21 and 24 have also been canceled without prejudice or disclaimer and the dependencies of various of the remaining claims amended. As the amendments do not add new matter, have already been searched in the previous claims, and simplify the issues for appeal, entry thereof after final is in order such that claims 1, 4, 5, 9, 10, 12, 14, 15, 17, 8, 22, 23, 25, 27-45, 47 and 48 are pending as shown above.

Rejection Withdrawn

Applicants note that the previous rejection of claims 1-14 and 43-45 under 35 U.S.C. § 112, 2nd paragraph was not reiterated and is therefore considered withdrawn.

35 U.S.C. § 112, 1st paragraph

Previous claims 1-12, 14 and 43-45 were rejected under 35 U.S.C. § 112, 1st paragraph as not enabled throughout their scope by the as-filed specification. (Final Office Action, paragraph 2). It was alleged that only compositions comprising an LTK63 protein and arginine phosphate and CHAPS are enabled. *Id.*

To the extent that the foregoing amendments do not obviate the rejection, Applicants traverse the rejection and supporting remarks.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). *See, also,* M.P.E.P. § 2164.01, citing *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989), which held that the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000.

The claims as pending are directed to compositions comprising AB5 CT and LT toxin proteins, a charged amino acid and a zwitterionic detergent. As acknowledged, the specification fully enables stabilizing of LTK63 with arginine phosphate and the zwitterionic detergent CHAPs. As previously noted, it would be routine for the skilled artisan to provide compositions comprising other LT or CT toxin in combination with a charged amino acid and a zwitterionic detergent inasmuch as LT holotoxins were, at the time of filing, known to be similar in structure and function. *See, e.g.,* pages 13-14, noting the well-characterized nature of CT and LT endotoxins and that these two proteins are "structurally, functionally and immunologically" similar, including in that LT and CT are immunologically cross-reactive. Thus, the skilled artisan would know that any LT or CT protein could be used in the claimed compositions.

Likewise, the skilled artisan, armed with the teachings of the specification and in view of the state of art, would know charged amino acids other than those exemplified (Arg) can be used to stabilize LT or CT proteins. *See, e.g.,* pages 18-28, including Table 8 on page 21 of the as-filed specification[1] showing that charged amino acids were tested and stabilized the claimed bARE proteins. Similarly, it would be routine in light of the as-filed specification to use any zwitterionic detergent to stabilize the LT or CT protein, as such agents were well known in the art and described in the specification (see, e.g., paragraphs [0107]-[0113] at page 22-page 23):

> [0107] Preferably the zwitterionic agent is a zwitterionic detergent.
>
> [0108] Zwitterionic detergents, also known as zwittergents are unique in that they offer the combined properties of ionic and non-ionic detergents. Like non-ionic detergents, the zwittergents, do not possess a net charge, they lack conductivity and electrophoretic mobility and do not bind to ion-exchange resins.
>
> [0109] Preferably the zwitterionic detergent is a bile salt derivative.
>
> [0110] As used herein, the term "bile salt derivative" refers to a derivative of cholesterol with a carboxylic acid. Examples of bile salt derivative include but are not limited to cholic acid and deoxycholic acid.
>
> [0111] Preferably the zwitterionic detergent, also known as a zwittergent, is selected from the group consisting of ASB-14, ASB-16, CHAPS, CHAPSO, DDMAB, DDMAU, Epigen BB Detergent, Lauryldimethylamine Oxide (LDAO), Zwittergent 3-08, 3-10, 3-12, 3-14, and 3-16 which are set out in FIG. 16. The

[1] Applicants note that Table 8 occurs on page 21 of the specification, before Table 7(b) on page 87 of the specification.

structures of CHAPS, CHAPSO and other Zwittergents outlined above is set out in FIG. 17 taken from "Detergents--A guide to the properties and uses of detergents in biological systems" by Srirama M Bhairi (2001) and available from Calbiochem (Doc no CB0068-401).

[0112] Preferably the uncharged detergent is a zwittergent such as CHAPS (3-(3-Cholamidopropyl)-dimethylammonio-1-propanesulfonate). CHAPS is a zwitterionic synthetic derivative of a bile salt. The structure of CHAPS is set out in FIG. 17. CHAPS is available from a number of commercial sources including Calbiochem, an affiliate of Merck and Sigma, Aldrich.

[0113] Without wishing to be bound by theory, zwittergents, such as CHAPS, are advantageous because they are less denaturing than the Zwittergent.RTM. 3-X series, possibly owing to their rigid steroid ring structure. Thus, zwittergents, such as CHAPS, may enhance the stable association of the A and B subunits.

[0114] Preferably the uncharged detergent is a zwittergent such as CHAPSO (3-(3-Cholamidopropyl)-dimethylammonio-2-hydroxypropanesulfonate). The CHAPSO structure is also set out in FIG. 17. CHAPSO is available from a number of commercial sources including Calbiochem, an affiliate of Merck and Sigma, Aldrich.

Thus, it would simply be a matter of routine experimentation for the skilled artisan to identify suitable charged amino acids and zwitterionic detergents other than those exemplified. Accordingly, withdrawal of the rejection is in order.

35 U.S.C. § 102

Pizza

Claims 1, 2, 6-8, 12-14 and 43-45 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent Publication No. 2002/0044939 (hereinafter "Pizza"). (Final Office Action, paragraph 4). It was alleged that Pizza teaches AB5-LTK63 and LTK 72 proteins that are analyzed under non-dissociating conditions which differentiate between integral an dissociated bARE class proteins. *Id.*

The pending claims are directed compositions comprising a soluble, substantially integral AB5 LT or CT holotoxin, a charged amino acid and a zwitterionic detergent. Pizza is silent as to both charged amino acids and zwitterionic detergents, as claimed. Thus, Pizza does not describe or demonstrate the specifically claimed composition and the rejection cannot be sustained.

Pronk

Claims 1, 2, 6-8, 12-14 and 43-45 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pronk et al. (1985) *J. Biol.. Chem.* 260(25):13580-13584 (hereinafter "Pronk"). (Final Office Action, paragraph 5).

As acknowledged, Pronk does not teach compositions comprising an LT or CT protein, a charged amino acid and a zwitterionic detergent. Accordingly, Pronk does not describe or demonstrate the claimed subject matter and withdrawal of the rejection is in order.

CONCLUSION

In view of the foregoing, Applicants submit that the claims are in condition for allowance.

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